Reactions with Mercaptans. V. Action of Aromatic Thiols on Furocoumarins, Furochromones, and 2-Aralkylidene-3(2*H*)-thianaphthenone-1,1-dioxides

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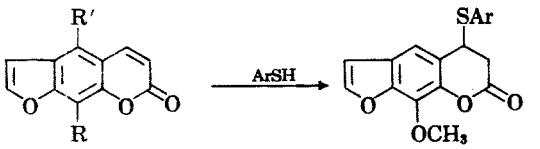
In conjunction with the study of the pharmacological action of sulfur-containing compounds,[1] we now have found that the addition products (IIa–b) are obtained upon treatment of xanthotoxin (Ia) with thiophenol and *p*-thiocresol, respectively, in the presence of piperidine. Structure II is assigned for the sulfides.[1] The unreac-



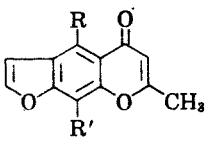
Ia, R = OCH_3, R' = H
b, R = $OCH_2CH{=}C(CH_3)_2$, R' = H
c, R = H, R' = OCH_3
d, R = OH, R' = $CH_2CH{=}C(CH_3)_2$

IIa, Ar = C_6H_5 b, Ar = $C_6H_4CH_3$-*p*

tivity of the unsaturated system in the furan ring in Ia may be deduced from the unreactivity of coumarilic acid and/or its methyl ester toward the action of thiophenol (*cf.* Experimental).

Treatment of bergapten (Ic) and imperation (Ib) with thiophenol under given experimental conditions results in the recovery of unchanged Ic and the formation of alloimperation (Id).[2]

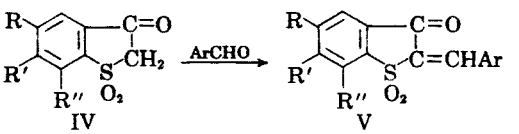
Khellin (IIIa) and visnagin (IIIb) undergo demethylation by the action of thiophenol and/or *p*-thiocresol under the described experimental conditions to give IIIc[3–5] and IIId, respectively.



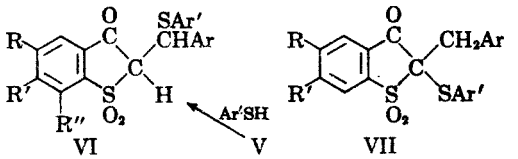
IIIa, R = R' = OCH_3
b, R' = H, R = OCH_3
c, R = OH, R' = OCH_3
d, R = OH, R' = H

Parallel experiments with phenol results in recovery of the unchanged IIIa. We believe that demethylation is to be connected with the methoxyl group in position 5, since IIIc is insoluble in alkali and is stable toward ethereal diazomethane.[5,6] Methylation of IIIc with diazomethane in the presence of methyl alcohol regenerates[7] IIIa.

Aromatic thiols now have been found to add to the double bond at position 2, which is conjugated with the unsaturated group in the newly prepared 2-aralkylidene-3(2*H*)-thianaphthenone-1,1-dioxide [prepared from the condensation of 3(2*H*)-thianaphthenone-1,1-dioxide (IV) with benzaldehyde] (V *cf.* Table I) in the absence of catalyst to yield the colorless thiol adducts[8] (*cf.* Table II), believed to have structure VI and not VII. Compound VIb, for example, dissolves in cold sodium hydroxide solution to give a yellow solution and is regenerated upon neutralization. It is decomposed when heated above its melting point to give Vb. The ease of removal of the addend indicates that the substance is the result of simple addition and that no unexpected reaction has occurred. Attempts to oxidize VIb with hydrogen peroxide in glacial acetic acid on the water bath also led to the formation of Vb.[9]



a, R = R' = R'' = H; Ar = C_6H_5
b, R = CH_3, R' = R'' = H, Ar = C_6H_5
c, R = R'' = H, R' = CH_3, Ar = C_6H_5
d, R = R' = H, R'' = CH_3, Ar = C_6H_5
e, R = R' = H, R'' = Cl, Ar = C_6H_5
f, R = R' = R'' = H, Ar = $C_6H_4OCH_3$-*p*



EXPERIMENTAL

Thiol adducts: General procedure. A mixture of 0.5 g. of the substance under investigation, 0.5 g. of the aromatic thiol, and a few drops of freshly distilled piperidine was warmed on a steam bath for 10 hr. in the case of Ia. In the case of Vb–f, the reaction mixture was heated at the stated temperature (*cf.* Table II) for 3 hr. in the absence of a catalyst.

(1) A. Mustafa, M. Kamel, M. A. Allam, A. H. E. Harhash, and A. E. A. A. Hassan, *J. Am. Chem. Soc.*, **78**, 5011 (1956).

(2) E. Späth and H. Holzen, *Ber.*, **68B**, 1123 (1935).

(3) Mukerjee and T. R. Seshadri, *Proc. Indian. Acad. Sci.*, **35A**, 323 (1952).

(4) H. Abu-Shadi and T. O. Soine, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 325 (1952).

(5) A. Schönberg and G. Aziz, *J. Am. Chem. Soc.*, **75**, 3265 (1953).

(6) The failure of phenolic hydroxyl group ortho or peri to a carbonyl group to react with diazomethane under normal conditions is a well-known example and this is of diagnostic value in establishing the structure of hydroxyflavones, -xanthones, etc. [*cf.* V. C. Farmer, N. F. Hays, and R. H. Thomson, *J. Chem. Soc.*, 3600 (1956)].

(7) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 746 (1946).

(8) A. Mustafa and S. M. A. D. Zayed, *J. Am. Chem. Soc.*, **79**, 3500 (1957).

(9) ω-*p*-Dinitrostyrene thiol adducts behave similarly when heated with hydrogen peroxide under the same conditions [*cf.* A. Mustafa, A. H. E. Harhash, and M. Kamel, *J. Am. Chem. Soc.*, **77**, 3860 (1955)].

TABLE I

2-ARALKYLIDENE-3(2*H*)-THIANAPHTHENONE-1,1-DIOXIDES (V)

Arylidene Deriv.[a]	Reaction Temp., °C.	M.P., °C.[b]	Yield, %	Solvent for Cryst.	Formula	Analysis					
						Carbon		Hydrogen		Sulfur	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
Vb	150	209	92	A (Pale yellow)	$C_{16}H_{12}O_3S$	67.61	67.54	4.23	4.02	11.27	11.10
Vc	160	210	78	A (Pink)	$C_{16}H_{12}O_3S$	67.61	67.38	4.23	4.13	11.27	11.21
Vd	160	158	75	B (Pale yellow)	$C_{16}H_{12}O_3S$	67.61	67.51	4.23	4.00	11.27	11.19
Ve	170	216	85	A (Brownish)	$C_{15}H_9ClO_3S$[c]	59.11	58.93	2.95	3.00	10.51	10.29
Vf	150	165	71	B (Yellow)	$C_{16}H_{12}O_4S$	64.00	63.89	4.00	3.85	10.67	10.36

[a] For the method of preparation, *cf.* A. Mustafa, S.M.A.D. Zayed (ref. 8). [b] All melting points are uncorrected. A, Acetic acid; B, ethyl alcohol. [c] Calcd.: Cl, 11.67. Found: 11.34.

The cooled reaction mixture was washed with light petroleum (b.p. 40–60°) and the resulting solid was crystallized from the proper solvent.

IIa formed colorless crystals from ethyl alcohol, m.p. 132°, in *ca.* 80% yield.

Anal. Calcd. for $C_{18}H_{12}O_4S$: C, 66.46; H, 4.00; S, 9.84. Found: C, 66.12; H, 4.00: S, 10.02.

It is soluble in hot benzene, but difficultly soluble in light petroleum and gives yellowish green color with concentrated sulfuric acid.

IIb formed colorless crystals from ethyl alcohol, m.p. 136°, in *ca.* 72% yield.

Anal. Calcd. for $C_{19}H_{14}O_4S$: C, 67.25; H, 4.42; S, 9.43. Found: C, 67.00; H, 4.49; S, 9.11.

It is soluble in hot benzene and gives an orange-yellow color with concentrated sulfuric acid.

IIa and IIb are insoluble in cold aqueous sodium hydroxide solution (10%), their alcoholic solutions give no color with ferric chloride, and are stable under normal conditions.

The thiol adducts (VI), listed in Table II, are colorless, soluble in hot benzene, but are difficultly soluble in ether, ethyl alcohol and in glacial acetic acid.

Action of potassium hydroxide on IIa. The thiol adduct (1 g.) was refluxed with 100 ml. of alcoholic potassium hydroxide solution (4%) for 4 hr. The cooled reaction mixture was poured into ice cold water, acidified with hydrochloric acid, and extracted with ether. The ethereal solution gave, on shaking with lead acetate solution, yellow crystals (*ca.* 0.25 g.) of the lead salt of thiophenol (melting point and mixed melting point[10]).

The ethereal solution, after thorough washing with water and drying, gave on evaporation a colorless solid (*ca.* 0.5 g.) which was identified as Ia (melting point and mixed melting point).

Thermal decomposition of VI ($R = CH_3$, $R' = R'' = H$, $Ar = Ar' = C_6H_5$). The thiol adduct (0.2 g.) was heated in a dry test tube at 140° (bath temperature) for 20 min. The cooled reaction mixture was crystallized from ethyl alcohol and identified as Vb (melting point and mixed melting point).

Action of thiophenol on Ib. A mixture of equimolecular amounts of Ib and thiophenol and few drops of piperidene was heated in an oil bath at (155–160°) for 3 hr. The cooled reaction mixture was washed with light petroleum (b.p. 40–60°) and the resulting solid was crystallized from benzene as colorless crystals of Id, m.p. 233°, not depressed when mixed with an authentic sample of Id;[2] yield, *ca.* 85%.

Anal. Calcd. for $C_{16}H_{14}O_4$; C, 71.11; H, 5.18. Found: C, 71.23; H, 5.09.

It is soluble in hot benzene and in aqueous sodium hydroxide solution (10%). Id is recovered unchanged when heated with thiophenol at 160°.

Attempted action of thiophenol on bergapten, coumarilic acid, and its methyl ester. A mixture of 0.5 g. of each of the above mentioned compounds, one gram of thiophenol, and few drops of piperidine was heated at 100° for 10 hr. When the reaction mixtures were worked up, the starting materials were recovered essentially unchanged (melting point and mixed melting point determinations).

Repeating the experiments at 140° for the same time period resulted in the recovery of the unchanged materials.

Demethylation effected with aromatic thiols. (*a*) *Partial demethylation of* IIIa. A mixture of 1 g. of IIIa, 2 g. of thiophenol, and a few drops of freshly distilled piperidine was heated at 100°. After 10 min. heating, the color of the reaction mixture changed to yellow and then heating was continued for 3 hrs. The cooled reaction mixture was washed with petroleum ether (b.p. 60–80°) and the residual solid was crystallized from ethyl alcohol as yellow crystals of IIIc m.p. 204°, not depressed when admixed with an authentic sample of IIIc; yield *ca.* 0.8 g.

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.41; H, 4.06. Found: C, 63.35; H, 4.11.

It is insoluble in aqueous sodium hydroxide solution (10%) and its alcoholic solution gives with aqueous ferric chloride a deep green color.

Treatment of IIIa with *p*-thiocresol as mentioned above led to the formation of 0.75 g. of IIIc.

(*b*) *Visnagin* (IIIb). The procedure was the same as in the case of IIIa and thiophenol. IIId was obtained, m.p. 155°. It is insoluble in sodium hydroxide solution.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.66; H, 3.70. Found: C, 66.58; H, 3.70.

Action of ethereal diazomethane on IIIc. To a suspension of 0.5 g. of IIIc in 30 ml. of dry ether and 2 ml. of methanol was added an ethereal solution of diazomethane (prepared from 4 g. of nitrosomethylurea). The cooled reaction mixture was kept aside in the ice chest for 24 hr., and then treated with another amount of freshly prepared ethereal diazomethane solution (from 4 g. of nitrosomethylurea). Then, it was left for 48 hr. at 0°. The solid, so obtained, was collected and the ethereal solution was allowed to evaporate slowly, whereas another crop of colorless crystals was obtained. The whole was crystallized from dilute methanol as color-

(10) B. H. Nicolet, *J. Am. Chem. Soc.*, 53, 3066 (1931).

TABLE II

THIOL ADDUCTS (VI) FROM 2-ARALKYLIDENE-3(2*H*)-THIANAPHTHENONE-1,1-DIOXIDES (V)

Arylidene Deriv.	Thiol Adduct Ar' =	Reaction Temp., °C.	M.p., °C.[a]	Yield, %	Solvent for Cryst.[c]	Color with H_2SO_4	Formula	Analysis % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sulfur Found	Sulfur Calcd.
Vb	C_6H_5	100	116	85	A	Orange-red	$C_{22}H_{18}O_3S_2$	67.00	66.87	4.56	4.32	16.24	16.01
	$C_6H_4CH_3$-*p*	130	156	82	B	Red	$C_{23}H_{20}O_3S_2$	67.65	67.24	4.90	4.73	15.69	15.31
Vc	C_6H_5	120	155	79	B	Orange	$C_{22}H_{18}O_3S_2$	67.00	66.91	4.56	4.55	16.24	15.89
	$C_6H_4CH_3$-*p*	130	182	76	B	Red	$C_{23}H_{20}O_3S_2$	67.65	65.67	4.90	4.84	15.69	15.56
Vd	C_6H_5	100	137	92	B	Red	$C_{22}H_{18}O_3S_2$	67.00	66.69	4.56	4.41	16.24	15.90
	$C_6H_4CH_3$-*p*	100	135	91	A	Red	$C_{23}H_{20}O_3S_2$	67.65	67.59	4.90	4.77	15.69	15.60
Ve	C_6H_5	120	150	87	B	Yellow	$C_{21}H_{15}ClO_3S_2$[b]	60.79	60.81	3.61	3.42	15.44	15.19

[a] Melting points are uncorrected. [b] Calcd. for Cl: 8.56. Found: Cl, 8.32. [c] A, Benzene–petroleum ether (b.p. 50–70°). B, Benzene.

less crystals, m.p. 153° and identified as IIIa (melting point and mixed melting point).

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Studies on 3-Acylcatechols

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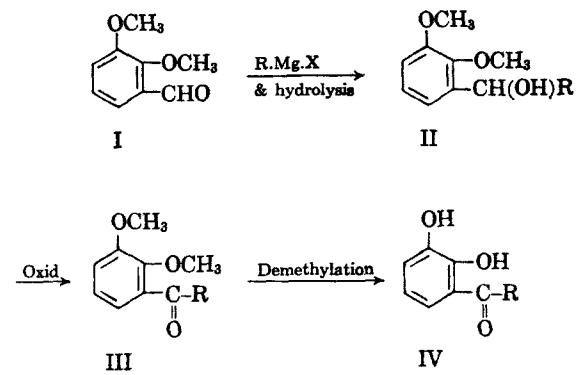
The methods available for the preparation of 3-acylcatechols, which are needed as starting materials in our work, are very limited. The most reliable method is that described by Krannichfeldt[1] for 2,3-dihydroxyacetophenone (IV, R= CH_3) according to the following scheme I–IV.



We have prepared 2,3-dihydroxypropiophenone (IV, R=C_2H_5) and 2,3-dihydroxybutyrophenone (IV, R= *n*-C_3H_7) according to the above scheme. These compounds are pale yellow in color, and give a green color with ferric chloride that changes to red by the addition of sodium carbonate solution, a characteristic color test for catechols.[2,3]

Miller, Hartung, Rock, and Crossley[4] referred to 2,3-dihydroxypropiophenone (IV, R=C_2H_5) as a by-product of the Fries rearrangement of the corresponding catechol diester. The melting point (102.5–103.5°) as reported by these authors[4] does not correspond to the melting point (53°) of the product which we have obtained. The position of the substituents in our products which are prepared by an orthodox method cannot be questioned. This leads us to doubt the correctness of the structure given to the by-product obtained by Miller *et al.*[4]

(1) H. V. Krannichfeldt, *Ber.*, **46**, 4017, 4018 (1913).

(2) Compare Paul Karrer, *Organic Chemistry*, Fourth English Edition, Elsevier Publ. Co., Inc., New York, N. Y., p. 435.

(3) A. Schönberg, W. I. Awad and G. A. Mousa, *J. Am. Chem. Soc.*, **77**, 3850 (1955).

(4) Ellis Miller, Walter H. Hartung, Henry J. Rock, and Frank S. Crossley, *J. Am. Chem. Soc.*, **60**, 7 (1938).